A timing-of-birth effect on multiple sclerosis clinical phenotype

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ABSTRACT **Background:** A month-of-birth (MOB) effect has been shown in multiple sclerosis (MS). **Methods:** Our χ^2 analyses looked at whether this MOB effect differed by MS phenotype ("bout onset," "primary progressive"). **Results:** The MOB effect was derived from "bout onset" MS patients (May/November ratio = 1.43; $\chi^2 = 17.32$, $df = 1$, $p = 0.000032$). **Conclusions:** An unspecified environmental effect in early development can influence both multiple sclerosis susceptibility and phenotype.
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Within multiplex and simplex families, it is common for multiple sclerosis (MS) outcome to be discordant for the pace of disability accumulation[1] as well as for the simplest of divisions of clinical phenotype, for example, primary progressive MS (PPMS) vs relapsing–remitting/bout onset MS (RRMS).[2] Factors determining MS phenotype have remained unpredictable and largely obscure with perhaps the exception of gender and age at onset.[3] Whereas female predominance is less pronounced and age at onset is later in PPMS compared with RRMS, our understanding of even these simple demographics is insufficient to infer a causal or definitive relationship.[4]

Given the steep drop-off in concordance for MS outcome between twins and nontwin siblings,[5] it is reasonable to suppose that genes will influence phenotype, but the role of early life environment in determining this has scarcely been considered. Recent observations of an increased MS concordance rate for dizygotic twins compared with nontwin siblings from the same families[5] and a maternal parent-of-origin influence[6] have pointed to the importance of gestational and very early life events in determining MS susceptibility. It has not been clear whether these are genetic or environmental or represent gene–environment interactions.

A factor influencing MS susceptibility that is more clearly environmental in origin has come from the study of month of birth (MOB) in which significantly fewer MS patients were born in November and significantly more in May.[7]

In this article, we examine the relationship between the MOB effect and MS phenotype.

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Table Distribution by month of birth for MS cases by phenotype and controls

MOB	No. (%) PPMS unaffected siblings	No. (%) PPMS	No. (%) RRMS unaffected siblings	No. (%) RRMS	% Population controls (1926–1970)
Jan	181 (8.12)	271 (8.13)	932 (8.07)	901 (7.86)	1,096,651 (8.02)
Feb	169 (7.58)	251 (7.53)	797 (6.90)	878 (7.66)	1,032,882 (7.55)
Mar	167 (7.49)	276 (8.28)	984 (8.52)	1,022 (8.91)	1,187,630 (8.68)
Apr	206 (9.24)	298 (8.94)	1,038 (8.98)	982 (8.57)	1,168,350 (8.54)
May	218 (9.78)	293 (8.79)	1,088 (9.42)	1,101 (9.60)	1,238,935 (9.06)
Jun	166 (7.44)	268 (8.04)	969 (8.39)	969 (8.45)	1,202,046 (8.79)
Jul	180 (8.07)	297 (8.91)	1,011 (8.75)	1,044 (9.11)	1,193,942 (8.73)
Aug	186 (8.34)	305 (9.15)	970 (8.40)	961 (8.38)	1,156,480 (8.46)
Sep	184 (8.25)	287 (8.61)	964 (8.34)	976 (8.51)	1,157,627 (8.47)
Oct	196 (8.79)	249 (7.47)	937 (8.11)	940 (8.20)	1,114,282 (8.15)
Nov	171 (7.67)	254 (7.62)	938 (8.12)	768 (6.70)	1,050,758 (7.68)
Dec	206 (9.24)	285 (8.55)	925 (8.01)	923 (8.05)	1,075,868 (7.87)
Total	2,230 (100)	3,334 (100)	11,553 (100)	11,465 (100)	13,675,451 (100)
May/Nov ratio	1.27	1.15	1.16	1.43	1.18

MS = multiple sclerosis; MOB = month of birth; PP = primary progressive; RR = relapsing-remitting.

METHODS **Study groups.** The Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) has been described in numerous publications.[5-7] Here, we focused on the CCPGSMS index cases for whom MOB was known for their unaffected siblings. For the analyses, we separated index cases into the following two groups[2]: 1) PPMS: primary progressive (previously "chronic progressive), with at least 1 year of relapse-free progression from onset of clinical symptoms; 2) RRMS: "bout onset" with the presence or absence of later progression (secondary progressive MS).

Analyses. MOB data for the Canadian population (Statistics Canada for 1926 through 1970) and unaffected CCPGSMS siblings of index cases were used as controls in our earlier study, which led to the work presented here.[7] In the current study, the unaffected sibling control group was divided according to whether the index case in the sibship had PPMS or RRMS. We measured the May/November birth month ratios for 1) PPMS index cases and their unaffected siblings, 2) RRMS and their unaffected siblings, 3) PPMS index cases and the Canadian population, and 4) RRMS index cases and the Canadian population. As the more stringent random selection of only one sibling control from each family made no difference to results in our previous publication,[7] here we included all unaffected sibs within sibships studied. The χ^2 test was used to compare the counts between groups of interest.

RESULTS **Study groups.** ***Index cases.*** Of 21,062 index cases with a diagnosis of probable/definite MS according to criteria[8] and a known MOB, sufficient data were available to classify 14,799 (70.3%) as either PPMS (n = 3,334) or RRMS (n = 11,465) with the remainder being as yet unclassified. These percentages are consistent with expectations from natural history data on MS.[1] Some index cases remain unclassified because they died or were lost to CCPGSMS follow-up prior to the accumulation of sufficient data.

Controls: Unaffected siblings of index cases. Complete information from the CCPGSMS database was available for 2,230 unaffected siblings of 831 PPMS index cases and 11,553 unaffected siblings of 4561 RRMS index cases (table).

Control: Canadian population (MOB data in percentage from Statistics Canada for 1926 through 1970). The table shows Canadian census data from Statistics Canada by MOB (number and percentage of the Canadian population born in each month) over this period that closely matches the birth years of the CCPGSMS index cases.

May births: Comparison of frequencies. *"Unaffected" sibling controls.* May births for PPMS index cases and their unaffected siblings did not differ significantly ($\chi^2 = 1.56$, $df = 1$). Similarly, 9.60% of RRMS index cases were born in May compared with 9.42% of their unaffected siblings. This difference was not significant ($\chi^2 = 0.23$, $df = 1$).

Canadian population controls. The 8.79% PPMS index cases were born in May, not significantly different compared with Canadian controls ($\chi^2 = 0.30$, $df = 1$). Also, 9.60% of RRMS index cases were born in May compared with 9.06% of Canadian controls ($\chi^2 = 4.11$, $df = 1$, $p = 0.043$).

November births: Comparison of frequencies. ***Unaffected sibling controls.*** The frequency of PPMS index cases born in November did not differ significantly from their unaffected siblings ($\chi^2 = 0.005$, $df = 1$) (data not shown in table). In contrast, 6.70% of RRMS index cases were born in November, significantly less than the 8.12% for their unaffected siblings ($\chi^2 = 16.92$; $df = 1$; $p = 0.000039$) (table).

Canadian population controls. RRMS index cases were significantly less often born in November (6.70%) compared with controls (7.68%) ($\chi^2 = 15.67$, $df = 1$, $p = 0.000076$). In contrast, the frequency of November births among PPMS index cases (7.62%) did not differ significantly from controls (7.68%) ($\chi^2 = 0.02$, $df = 1$).

MOB distributions: May/November birth ratio. The May/November birth ratios for RRMS, PPMS, and Canadian controls were 1.43, 1.15, and 1.18, respectively. There was a significant difference between the birth ratios for RRMS and Canadian controls ($\chi^2 = 17.32$, $df = 1$, $p = 0.000032$), with the former group being born less often in November. The birth ratios for PPMS and Canadian controls were nearly identical ($\chi^2 = 0.065$, $df = 1$). The birth ratios for PPMS and RRMS differed significantly ($\chi^2 = 4.95$, $df = 1$, $p = 0.026$). The May/November birth ratios for the unaffected siblings of PPMS index cases and RRMS index cases were 1.27 and 1.16, respectively ($\chi^2 = 0.72$, $df = 1$). There was a significant difference between the birth ratios for RRMS and their unaffected siblings ($\chi^2 = 10.70$, $df = 1$, $p = 0.00107$), again with the RRMS being less often born in November. The May/November ratios for PPMS and their unaffected siblings were very similar ($\chi^2 = 0.56$, $df = 1$).

DISCUSSION

The data presented here for Canada demonstrate that the November nadir previously reported for MS susceptibility is derived entirely from individuals with RRMS. These data as well as our earlier work[1] now demonstrate that MS phenotype and susceptibility are likely influenced by factors that must occur during gestation or very shortly after birth. Taken together, the two Canadian studies on MOB and MS demonstrate that in a geographic area characterized by distinct seasonality, early life environmental factor(s) can influence both disease susceptibility and clinical course. These observations are not easily explained at present, although we have proposed a role for a broad population factor. Maternal vitamin D deficiency and some other sunlight-related effect in the genesis of the MOB observations are plausible candidates.[7] Nevertheless, these remain hypotheses, and there are undoubtedly other mechanisms by which birth timing might influence or be associated with both MS susceptibility and outcome. However, "gender" and "age at onset" aside, this may be the first observation to make a meaningful differentiation among risk factors for PPMS and RRMS.

These findings are consistent with the findings of a recent Sardinian study[9] in which space clustering was significant in early childhood but most markedly in individuals who had bout onset or RRMS. As well, a changing sex ratio strongly related to year of birth has been reported for this same Canadian population.[10]

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